Characteristics and clinical role of bronchoscopy in diagnosis of childhood endobronchial tuberculosis

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Background: **Endobronchial tuberculosis (EBTB) is the most frequent complication of primary pulmonary tuberculosis (PTB) in children. The aim of the study was to analyze characteristics and clinical role of bronchoscopy in diagnosis of childhood EBTB.**

Methods: **A retrospective, descriptive study was undertaken in 157 children with EBTB undergone flexible bronchoscopy (FB) between January 2006 and June 2014.**

Results: **The median age of the enrolled patients was 3.4 years, with 73.2% of patients under five years old. The most common subtype was tumorous type (145/157, 92.4%). If only involved bronchus were considered, the common affected sites were right middle lobe bronchus (49/228, 21.5%), left upper lobe bronchus (41/228, 18.0%), right upper lobe bronchus (41/228, 18.0%), right main bronchus (35/228, 15.4%), respectively. Children younger than five years old were at higher risk to have multiple endobronchial lesions (P=0.044), with an odds ratio of 2.313 (95% confidence interval: 1.009-5.299). Before the bronchoscopy, only 16 (10.2%) patients were highly suspected of EBTB, while the others were diagnosed as PTB without EBTB (69.4%), or misdiagnosed as pneumonia or foreign body aspiration (20.4%) on admission.**

Conclusions: **The patients under five years old are at high risk to progress to EBTB and have multiple endobronchial lesions. The most frequent subtype of EBTB in children is tumorous type. The lesions are seen in the right bronchial system more frequently. FB should be performed to detect the endobronchial lesions in suspected patients as soon as possible.**

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Key words: **diagnosis; endobronchial tuberculosis; flexible bronchoscopy**

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Introduction

It is reported that 46% of tuberculosis in children is primary pulmonary tuberculosis (PTB).[1] Endobronchial tuberculosis (EBTB) is the most frequent complication of PTB in children,[2] accounting for more than 40% of PTB cases.[3-5] The severe sequelae of EBTB, such as tracheobronchial stenosis or obstruction, may lower the quality of life or even result in death in children. Early detection and effective treatment of EBTB are crucial to avoid severe complications.

However, the diagnosis of EBTB is challenging due to the nonspecific clinical manifestations. Compared with the regular approaches, flexible bronchoscopy (FB) plays an important role in diagnosing childhood EBTB. It not only offers a rapid diagnosis by directly detecting the endobronchial lesions related to EBTB, but also provides samples for etiology and pathological investigations.

Revelation of the bronchoscopy characteristics is very helpful for the diagnosis of EBTB. But studies on the classifications and the clinical manifestations of EBTB are relative rare in children. Herein, we performed a retrospective, descriptive study to determine the bronchoscopy characteristics and the clinical role of FB in diagnosing childhood EBTB.

Methods

Study population

The patients enrolled in this study were 14 years of age and younger, who were admitted to Beijing Children's

Hospital between January 2006 and June 2014. Demographical and clinical characteristics were obtains from medical records. The indications for performing FB and the diagnostic criteria of EBTB were shown in Table 1, which is in accordance with the guideline recommended by Chinese Medical Association.[6] The classification of bronchoscopy subtypes followed the recommendations of Chung et al (Table 1).[7] Ethics approval was obtained from the Ethics Committee of Beijing Children's Hospital.

Statistical analyses

Categorical variables were compared using Chi-square test. SPSS version 13.0 was used for statistical analyses. All statistical hypothesis tests were two-sided, and *P* values less than 0.05 were considered statistically significant.

Table 1. Indications for FB, diagnostic criteria and classification of subtypes of EBTB

Parameters	Contents
Indications for FB	1) Clinical manifestations of PTB is not in conformity with the size and severity of pulmonary lesions; 2) Pulmonary lesions responsive to anti-tuberculosis treatment, but clinical presentation (symptoms or signs) without improvement; 3) During anti-tuberculosis treatment, pulmonary lesions enlarged, accompany with endobronchial spread lesions or tension cavities; 4) X ray of PTB patients suggested the presence of obstructive pneumonia, pulmonary atelectasis localized emphysema; 5) Chest CT scan, high resolution CT and multi-dimension reformation of PTB patients suggested the roughness of bronchial/trachea wall, or stenosis/obstruction of subsegmental bronchus; 6) Clinical manifestations (chronic persistent cough, hemoptysis, dyspnea, and so on) exist, but etiology is unclear.
Diagnostic criteria	1) Clinical presentation (symptoms or signs) and responsive to anti-tuberculosis treatment; 2) Sputum smear for acid-fast Mycobacterium was positive, or *Mycobacterium tuberculosis* culture was positive; 3) Chest radiography and computed tomography scan changes; 4) Purified protein derivative tuberculin skin test (using 5 TU) was positive; 5) Bronchoscopically visible bronchial lesions 6) Bronchoalveolar lavage for acid-fast *Mycobacterium* was positive; 7) Biopsy result was positive. The diagnosis can be confirmed if a patient meets the criteria 5) and 6), or 5) and 7), or 5) and 2). The patient was diagnosed as highly probable for EBTB if he/she meets the criteria 1) and 2) and 3), or 1) and 3) and 4), or 2) and 3), or 3) and 4), or 5) or 6) or 7)
Subtypes of EBTB	1) Actively caseating; 2) Edematous-hyperemic; 3) Fibrostenotic; 4) Tumorous; 5) Granular; 6) Ulcerative; 7) Nonspecific bronchitics.

FB: flexible bronchoscopy; EBTB: endobronchial tuberculosis; PTB: primary pulmonary tuberculosis; CT: computed tomography.

Results

Demographic and clinical information

A total of 189 children with EBTB were examined using FB, in which 157 with complete clinical information were enrolled in this study (Table 2). Among them, 75 were confirmed EBTB patients, in which 26 met the diagnostic criteria 5) and 6), eight met the criteria 5) and 7), and 41 met the criteria 5) and 2). The other 82 patients were diagnosed as highly probable EBTB, in which all 82 met the criteria 1) and 5), 66 also met the criteria 4), and 12 also met the criteria 3).

There were 115 (73.2%) patients under 5 years old. The median age of the enrolled patients was 3.4 years (interquartile range: 0.5-0.9 years) with the age ranging from 0.2 to 14 years. One hundred and five (66.9%) patients were male. The common symptoms on presentation were cough (123/157, 78.3%) and fever (117/157, 74.5%), followed by shortness of breath or wheezing (34/157, 21.7%). Ninety-six (61.1%) patients had a Bacillus Calmette-Guérin scar, and 53 (33.8%) had a history of contact with active tuberculosis patients. Tuberculin skin test was positive in 122 patients (77.7%). Culture for *Mycobacterium tuberculosis* was positive in 41 (26.1%) patients, in

Table 2. Clinical characteristics of patients with EBTB (*n*=157)

Characteristics	Value
Age (y), mean±standard deviation	3.4±3.7
Gender, female/male	52/105
Symptoms, *n* (%)	
Fever	117 (74.5)
Cough	123 (78.3)
Shortness of breath or wheezing	34 (21.7)
BCG scar, *n* (%)	
Yes	96 (61.1)
No	61 (38.9)
Contact history, *n* (%)	
Yes	53 (33.8)
No	104 (66.2)
Complications, *n* (%)	
EBTB+PTB	157 (100)
EBTB+PTB+disseminated TB	14 (8.9)
EBTB+PTB+abdominal TB	8 (5.1)
EBTB+PTB+tubercularmeningitis	6 (3.8)
EBTB+PTB+tuberculous pleurisy	3 (1.9)
Mycobacterium tuberculosis culture, *n* (%)	
BALF	28 (17.8)
Gastric aspirate	6 (3.8)
Sputum	3 (1.9)
BALF+gastric aspirate+sputum	1 (0.6)
BALF+gastric aspirate	2 (1.3)
BALF+sputum	1 (0.6)

FB: flexible bronchoscopy; EBTB: endobronchial tuberculosis; PTB: primary pulmonary tuberculosis; BCG: Bacillus Calmette-Guérin; BALF: bronchoalveolar lavage fluid.

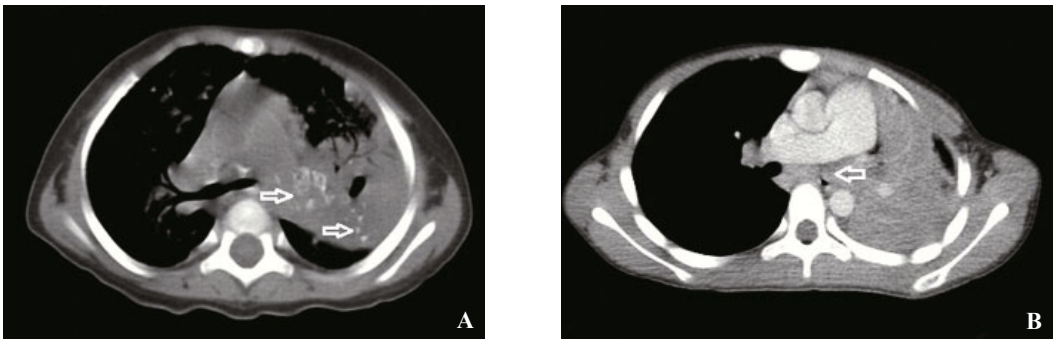

Fig. 1. A: CT showing the enlarged mediastinal lymph nodes, and the calcification in the mediastinal lymph nodes and pulmonary parenchyma (arrows) in a child with primary tuberculosis; **B**: CT showing the left main bronchus stenosis with tuberculous pulmonary parenchyma in the left upper lung field (arrow), which indicates endobronchial tuberculosis. CT: computed tomography.

which 32 samples were bronchoalveolar lavage fluid (BALF), 9 were gastric aspirate, and 5 were sputum, with 4 patients having 2 or 3 positive samples. Acid-fast bacilli tests of BALF were positive in 26 (16.6%) patients.

All 157 children were diagnosed with PTB. Among these children, 14 (8.9%) of them were still had complications with disseminated tuberculosis, 8 (5.1%) with abdominal tuberculosis, 6 (3.8%) with tubercular meningitis, and 3 (1.9%) with tuberculous pleurisy.

Based on chest X-ray or computed tomography (CT), pulmonary consolidation had been found in 156 cases (99.4%), mediastinal or hilarlymph nodes enlargement in 94 cases (59.9%), mediastinal or hilar lymph nodes or pulmonary parehchyma calcification in 35 cases (22.3%) (Fig. 1A). Meanwhile, 85 (54.1%) cases were suggested to have airway involved signs including pulmonary atelectasis (28/157, 17.8%), central airway stenosis (25/157, 15.9%), obstructive pneumonia (25/157, 15.9%), emphysema (18/157, 11.5%), and the roughness of bronchial wall (2/157, 1.3%).

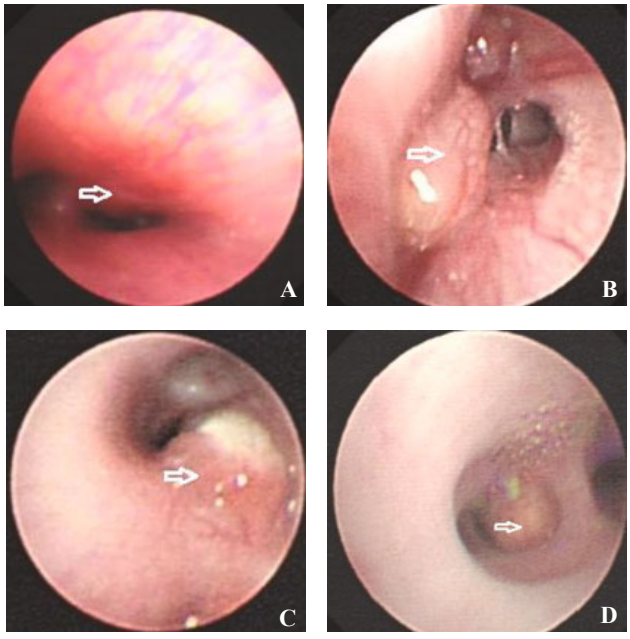

Fig. 2. **A**: Nonspecific bronchitic type EBTB with extrabronchial compression in right lower lobe bronchus (arrow); **B**: Tumorous type EBTB in right upper lobe bronchus (arrow); **C**: Tumorous type EBTB coating with whitish cheese-like material in right main bronchus (arrow); **D**: Tumorous like lesion in subsegmental bronchus of left lower lobe (arrow). EBTB: endobronchial tuberculosis.

Bronchoscopic characteristics of EBTB

According to the classification of EBTB advocated by Chung et al,[7] tumorous type (145/157, 92.4%) was the most common subtype. Six patients (3.8%) whose endobronchial lesions were only mild mucosal swelling and/or hyperemia were classified as nonspecific bronchitic type (Fig. 2), and 3 of them progressed to the tumorous type during the antituberculosis chemotherapy. There were still 6 patients (3.8%) whose endobronchial lesions cannot be exactly classified into any subtype mentioned above, even though they were similar in the appearance with the tumorous type (Fig. 2D).

Total 101 (64.3%) patients had single lesion in the bronchial wall, 44 patients (28.0%) had 2 lesions, 9 (5.7%) had 3 lesions and 3 (1.9%) had 4 lesions. The common involved bronchus in patients with single lesion were left upper lobe bronchus (27/101, 26.7%), right upper lobe bronchus (20/101, 19.8%), right middle lobe bronchus (16/101, 15.8%). While in the patients with 2 lesions, the common simultaneously involved bronchus were right upper lobe and right middle lobe bronchus (9/44, 20.4%), right main and right middle lobe bronchus (9/44, 20.4%). In other way, if only involved bronchus were all considered, the common affected sites were right middle lobe bronchus (49/228, 21.5%), left upper lobe bronchus (41/228, 18.0%), right upper lobe bronchus

(41/228, 18.0%), right main bronchus (35/228, 15.4%), respectively. The patients under 5 years old were at higher risk to have multiple endobronchial lesions (P=0.044), with an odds ratio of 2.313 (95% confidence interval: 1.009-5.299). Seventy-four (47.1%) children had central airway stenosis by extrinsic compression of enlarged intrathoracic tuberculous lymph nodes.

Role of FB on diagnosis of EBTB

At admission, based on symptoms and radiological results, 32 (20.4%) patients were misdiagnosed as pneumonia or foreign body aspiration, 109 (69.4%) were diagnosed as PTB without EBTB, and only 16 (10.2%) were highly suspected of EBTB (Figs. 1B and 2C). After the examination of FB, all 157 children were determined to have EBTB by the bronchoscopic findings.

Discussion

In our study, EBTB is not so rare in children especially in young children less than 5 years old. In addition, multiple endobronchial lesions are more often seen in patients under 5 years old, which suggests that younger children are a vulnerable group for development of EBTB, likely due to the immature of the childhood immune system to control the progress of the disease. Thus, more attention should be paid for infants and young children with a suspicion for respiratory illness.

The clinical manifestations of childhood EBTB are often nonspecific. Although irritable cough may be an important feature of EBTB,[8] it is also frequently seen in other diseases, such as asthma, foreign body aspiration, pneumonia, and so on. EBTB is often ignored and rapidly progress to caseous necrosis and/or granulation.[9] In this study, the common symptoms were cough (78.3%), fever (74.5%), shortness of breath or wheezing (21.7%), of which persistent cough, shortness of breath or wheezing should be the important indications for bronchoscopy. Before the bronchoscopy, only 16 (10.2%) patients were highly suspected of EBTB, while the others were diagnosed as PTB without EBTB (69.4%), or misdiagnosed as pneumonia or foreign body aspiration (20.4%) on admission. Therefore, the important role of FB in the diagnosis of EBTB should be highly emphasized.

Usually, the radiological findings is quite useful in diagnosing PTB, but it has certain disadvantages in recognizing EBTB, as intrabronchial lesions might be undetectable by imaging unless airway obstruction occurred showing direct or indirect signs, such as pulmonary atelectasis, emphysema, airway stenosis, obstructive pneumonia, and roughness of bronchial wall. In our study, 47.1% of cases had central airway stenosis observed by FB, but only 15.9% of cases were identified by chest imaging. So if the PTB children meet the indications will undergo FB to confirm the bronchial involvement.

Until now, there is no standard classification of EBTB specific for children. Thus we took the widely used classification system of EBTB advocated by Chung et al.[7] In this study, tumorous type (92.4%) was the most common subtype, followed by nonspecific bronchitic type (6 cases, 3.8%). In addition, 3 cases with nonspecific bronchitic type progressed to the tumorous type during the antituberculosis chemotherapy. While Chung et al[7] reported that in adults with EBTB, the actively caseating type (43.0%) was the most common form, with tumorous type accounting for only 10.5%. The difference may be due to that primary PTB is the most common type in children and childhood EBTB mostly originate from the penetration of an adjacent tuberculous lymph node through the bronchial wall.[10] However, there were other 6 (3.8%) patients with caseous pneumonia whose endobronchial lesions in subsegmental bronchus adjacent to tuberculous pulmonary parenchyma cannot be exactly classified into any subtype mentioned above. It was more like a fistula between the caseous pulmonary parenchyma and the bronchial wall. The caseous pneumonia in children often occur as part of PTB, and pulmonary parehchyma calcification is a symbol of it. Further study needs to be done to explore how the endobronchial lesions occur in children with caseous pneumonia.

Similar with previous studies,[2,3] we observed that the lesions were seen in the right bronchial system more frequently, no matter in patients with single or multiple lesions. The results were consistent with the locations of the enlarged lymph nodes in mediastinal or hilar seen in the CT scan or detected by bronchoscopy through the signs of external compressive central airway stenosis. The right middle lobe bronchus is very common involved lesion in this study. However, it is relative rare in other previous studies.[11-13] It is speculated that childhood EBTB mostly originates from the penetration of an adjacent tuberculous lymph node through the bronchial wall,[10] so the right middle lobe bronchus which is adjacent to the location of the mediastinal lymph nodes is the most commonly affected site. Although the pathogenesis is not very clear, it provides some useful information for the various manifestation of childhood EBTB.

In conclusion, the younger patients, especially those under 5 years, are at high risk to progress to EBTB and have multiple endobronchial lesions. The most frequent subtype of EBTB in children is tumorous type. The lesions were seen in the right bronchial system more

frequently, no matter the right upper lobe, right middle lobe and right main bronchus. FB should be performed to detect the endobronchial lesions in suspected patients as soon as possible.

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Contributors: Jiao AX designed the study, performed the flexible bronchoscopy and drafted the initial manuscript. Sun L carried out the initial analyses and drafted the initial manuscript. Liu F, Rao XC, Ma YY, Liu XC and Xu BP collected the data, finished the clinical work and revised the manuscript. Shen C and Shen AD collected the data and revised the manuscript. Shen KL supervised data collection, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

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